Receptor for advanced glycation end products up-regulation in cerebral endothelial cells mediates cerebrovascular-related amyloid β accumulation after Porphyromonas gingivalis infection

曽, 凡

（様式６－２）

氏　　名	曽　凡
論　文　名	Receptor for advanced glycation end products up-regulation in cerebral endothelial cells mediates cerebrovascular-related amyloid ß accumulation after *Porphyromonas gingivalis* infection （脳内皮細胞における終末糖化産物受容体の亢進は、*Porphyromonas gingivalis* 感染による脳血管が関与するアミロイドβの蓄積を誘導する）
論文調査委員	主　査　　九州大学　　教授　　山下　喜久 副　査　　九州大学　　教授　　重村　憲徳 副　査　　九州大学　　教授　　清島　保

論　文　審　査　の　結　果　の　要　旨

Cerebrovascular-related amyloidogenesis is found in over 80% of Alzheimer's disease (AD) cases, and amyloid β (Aβ) generation is increased in the peripheral macrophages during infection of *Porphyromonas gingivalis* (*Pg*), a causal bacterium for periodontitis. In this study, we focused on receptor for advanced glycation end products (RAGE), the key molecule involves in Aβ influx after *Pg* infection to test our hypothesis that Aβ transportation from periphery into the brain, known as “Aβ influx,” is enhanced by *Pg* infection. Using cultured hCMEC/D3 cell line, in comparison to uninfected cells, directly infection with *Pg* (multiplicity of infection, MOI = 5) significantly increased a time-dependent RAGE expression resulting in a dramatic increase in Aβ influx in the hCMEC/D3 cells; the *Pg*-up-regulated RAGE expression was significantly decreased by NF-κB and Cathepsin B (CatB)-specific inhibitors, and the *Pg*-increased IκBα degradation was significantly decreased by CatB-specific inhibitor. Furthermore, the *Pg*-increased Aβ influx was significantly reduced by RAGE-specific inhibitor. Using 15-month-old mice (C57BL/6JJmsSlc, female), in comparison to non-infection mice, systemic *Pg* infection for three consecutive weeks (1×10^8 CFU/mouse, every 3 days, intraperitoneally) significantly increased the RAGE expression in the CD31-positive endothelial cells and the Aβ loads around the CD31-positive cells in the mice's brains. The RAGE expression in the CD31-positive cells was positively correlated with the Aβ loads. These observations demonstrate that the up-regulated RAGE expression in cerebral endothelial cells mediates the Aβ influx after *Pg* infection, and CatB plays a critical role in regulating the NF-κB/RAGE expression.

The study well supports the conclusion that *Pg* infection up-regulates RAGE expression in cerebral endothelial cells mediating the amyloid β influx through NF-κB activation. The candidate is worth to be given the degree of Doctor of Philosophy.